Autoimmun Rev. 2005 Apr;4(4):195-200. Epub 2004 Nov 17. Related Articles, Links

Clinical and pathological characteristics of Mikulicz's disease (IgG4-related plasmacytic exocrinopathy).

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Mikulicz's disease (MD) has been considered part of primary Sjogren's syndrome (SS) since Morgan's report in 1953. MD **represents a unique condition involving enlargement of the lacrimal and salivary glands, as is also seen in SS; however, MD is characterized by few autoimmune reaction and its good responsiveness to glucocorticoid.** Recent reports have shown that the frequency of apoptosis in glands of MD patients is lower when compared with SS. This phenomenon reflects the histologically reversible gland secretion in MD. Elevated IgG4 concentrations in the serum and prominent infiltration by plasmacytes expressing IgG4 in the lacrimal and salivary glands have also been confirmed in MD. Plasma cells expressing IgG4 are also detected in lymph nodes and bone marrow. MD may be a systemic disease, rather than a lacrimal and salivary gland disease. We here propose the new entity "IgG4-related plasmacytic exocrinopathy" and expect future development with regard to its relationship with autoimmune pancreatitis, which similarly presents elevated serum IgG4 levels.

Publication Types:

- Review

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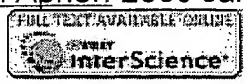
J Clin Apher. 2006 Jan 19; [Epub ahead of print] Related Articles, Links



Lymphocytapheresis in the treatment of psoriasis vulgaris.

Liumbruno GM, **Centoni PE**, **Molfettini P**, **Ceretelli S**, **Ceccarini M**, **Bachini L**, **Pomponi A**, **Bagnoni G**, **Vitolo M**, **Eberle O**, **Biondi A**, **Sodini ML**.

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Psoriasis is a common autoimmune chronic inflammatory skin disease that affects approximately 2% of the world's population; fundamental for its immunopathogenic mechanism is secretion of type 1 (Th1) cytokines by T cells and their activation. Since cytapheresis has been widely applied to autoimmune disorders, emphasizing the recently reported results of granulocyte and monocyte adsorption apheresis in psoriasis, a small series of psoriasis vulgaris (PV) patients underwent lymphocytapheresis (LCA) with the aim to remove lymphocytes. Five patients were submitted to weekly LCA. The severity of the disease had been evaluated through psoriasis area and severity index (PASI) score before LCA and one week after the last apheresis. PASI score before: patient A: 66; patient B: 33; patient C: 50; patient D: 56; patient E: 29. All the patients showed improvement of skin lesions. PASI score after LCA: patient A: 24; patient B: 8; patient C: 5; patient D: 36; patient E: 2.1. No side effects linked to apheresis were reported. LCA seems to produce interesting results in PV, and PASI improvement related to apheresis is clinically significant. Further studies to address its mechanism of action and potential long-term side effects are needed. It could become a valuable therapeutic alternative or a complementary tool, which might even be used to reduce the dosages of conventional pharmacological therapies adopted for this chronic disease. J. Clin. Apheresis 2006.

PMID: 16425186 [PubMed - as supplied by publisher]

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Clin Exp Immunol. 2005 Dec;142(3):411-8. Related Articles, Links

Defective signalling in salivary glands precedes the autoimmune response in the non-obese diabetic mouse model of sialadenitis.

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The spontaneous non-obese diabetic (NOD) mouse model of Sjogren's syndrome provides a valuable tool to study the onset and progression of both the autoimmune response and secretory dysfunction. Our purpose was to analyse the temporal decline of salivary secretion in NOD mice in relation to the autoimmune response and alterations in various signalling pathways involved in saliva secretion within each salivary gland. A progressive loss of nitric oxide synthase activity in submandibular and parotid glands started at 12 weeks of age and paralleled the decline in salivary secretion. This defect was associated with a lower response to vasoactive intestinal peptide in salivary flow rate, cAMP and nitric oxide/cGMP production. No signs of mononuclear infiltrates or local cytokine production were detectable in salivary glands in the time period studied (10-16 weeks of age). **Our data support a disease model for sialadenitis in NOD mice in which the early stages are characterized by defective neurotransmitter-mediated signalling in major salivary glands that precedes the autoimmune response.**

PMID: 16297151 [PubMed - indexed for MEDLINE]

Sperelakis N. ed. Cell Physiology Sourcebook, 3rd ed. 2001 Chapter 10, 167-177.

Am J Physiol Gastrointest Liver Physiol. 2006 Jan 6; [Epub ahead of print]

Parietal Cell Hyperstimulation and Autoimmune Gastritis in Cholera Toxin Transgenic Mice.

Lopez-Diaz L, **Hinkle KL**, **Jain RN**, **Zavros Y**, **Brunkan CS**, **Keeley T**, **Eaton KA**, **Merchant JL**, **Chew CS**, **Samuelson LC**.

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The stimulation of gastric acid secretion from parietal cells involves both intracellular calcium and cAMP signaling. To understand the affect of increased cAMP on parietal cell function we engineered transgenic mice expressing cholera toxin, an irreversible stimulator of adenylate cyclase. The parietal cell-specific H(+), K(+)-ATPase beta-subunit promoter was used to drive expression of the cholera toxin A1 subunit (Ctox). Transgenic lines were established and tested for Ctox expression, acid content, plasma gastrin, tissue morphology and cellular composition of the gastric mucosa. Four lines were generated, with Ctox 7 expressing ~50-fold higher Ctox than the other lines. Enhanced cAMP signaling in parietal cells was confirmed by observation of hyperphosphorylation of the protein kinase A-regulated proteins LASP-1 and CREB. Basal acid content was elevated and circulating gastrin was reduced in Ctox transgenic lines. Analysis of gastric morphology revealed a progressive cellular transformation in Ctox 7. Expanded patches of mucous neck cells were observed as early as 3 months of age, and by

15 months extensive mucous cell metaplasia was observed in parallel with almost complete loss of parietal and chief cells. Detection of anti-parietal cell antibodies, inflammatory cell infiltrates, and increased expression of the Th1 cytokine interferon-gamma in Ctox 7 mice suggested that autoimmune destruction of the tissue caused atrophic gastritis. Thus, constitutively high parietal cell cAMP results in high acid secretion and a compensatory reduction in circulating gastrin. **High Ctox in parietal cells can also induce progressive changes in the cellular architecture of the gastric glands corresponding to the development of anti-parietal cell antibodies and autoimmune gastritis.**

PMID: 16399875 [PubMed - as supplied by publisher]

1: Cells Tissues Organs. 2003;174(1-2):26-33.

Related Articles, Links

Full Text

Nitric oxide in experimental joint inflammation. Benefit or detriment?

Wahl SM, McCartney-Francis N, Chan J, Dionne R, Ta L, Orenstein JM.

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The host response to infection or injury initiates a cascade of events involving recruitment of leukocytes and the release of multiple inflammatory mediators. One of these mediators, nitric oxide (NO), not only represents an important microbicidal agent in host defense, but also functions as a biological signaling and effector molecule in inflammation and immunity. However, overproduction of NO can be autotoxic and contribute to tissue damage and has been implicated in pathogenesis of tumors, and infectious, autoimmune and chronic degenerative diseases. NO is generated via constitutive and inducible nitric oxide synthases (iNOS) which catalyze the oxidation of a guanidino nitrogen associated with L-arginine. Whereas endothelial NOS (eNOS) and neuronal NOS (nNOS) are constitutively expressed, iNOS is transcriptionally induced by bacterial constituents and inflammatory mediators, including TNF alpha and IL-1. In an experimental model of bacterial component-induced joint inflammation and tissue degradation, functionally distinct roles of the constitutive NOS and iNOS were demonstrated. Following systemic delivery of an arthritogenic dose of streptococcal cell walls (SCW), these bacterial peptidoglycan-polysaccharide complexes disseminate and target the peripheral joints, liver and spleen of the treated animals. Following deposition of the SCW in the peripheral joints, an initial innate inflammatory response to the bacterial components progresses into an adaptive immune response with the recruitment and activation of mononuclear phagocytes and T lymphocytes. With the release of cytokines and inflammatory mediators, there is an upregulation of gene expression for iNOS, but not the constitutive nNOS or eNOS. Nonetheless, the constitutive

NOS isoforms, regulated by calcium fluxes and interaction with calmodulin, may also enhance NO production. Increased release of NO was detected not only in the synovium, but also in the circulation, and plasma levels of nitrate plus nitrite, the stable products of NO reactions, correlated with disease progression. Following inhibition of NO production with nonspecific NOS inhibitors, such as N(G)-monomethyl-L-arginine, which target all three isoforms, there is a striking therapeutic benefit with reduced signs and symptoms of erosive arthritis. In contrast, selective targeting of iNOS with N-iminoethyl-L-lysine resulted in exacerbation of the synovial inflammation and degradation of joint structures. Based on these data, it appears that the constitutive isoforms of NOS contribute to the pathophysiology of the arthropathy, and that induced NOS and NO may function, in part, in a protective pathway. Moreover, the suppression of NO following treatment with TNF alpha antagonists results in reduced inflammation and the associated synovial pathology. Collectively, these data implicate discrete roles for the NOS isoforms in the emergence of local tissue pathology and underscore the need to define the specific pathways that are being targeted for interventional strategies.

Publication Types:

- Review

PMID: 12784039 [PubMed - indexed for MEDLINE]

1: J Immunol. 2003 May 1;170(9):4441-9. Related Articles, Links

A pyrazole derivative, YM-58483, potently inhibits store-operated sustained Ca2+ influx and IL-2 production in T lymphocytes.

Ishikawa J, Ohga K, Yoshino T, Takezawa R, Ichikawa A, Kubota H, Yamada T.

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In nonexcitable cells, Ca(2+) entry is mediated predominantly through the store depletion-dependent Ca(2+) channels called store-operated Ca(2+) (SOC) or Ca(2+) release-activated Ca(2+) channels. YM-58483, a pyrazole derivative, inhibited an anti-CD3 mAb-induced sustained Ca(2+) influx in acute T cell leukemia, Jurkat cells. But it did not affect an anti-CD3 mAb-induced transient intracellular Ca(2+) increase in Ca(2+)-free medium, nor anti-CD3 mAb-induced phosphorylation of phospholipase Cgamma1. It was suggested that YM-58483 inhibited Ca(2+) influx through SOC channels without affecting the TCR signal transduction cascade. Furthermore, YM-58483 inhibited thapsigargin-induced sustained Ca(2+) influx with an IC (50) value of 100 nM without affecting membrane potential. YM-58483 inhibited by 30-fold the Ca(2+) influx through SOC channels compared with voltage-operated Ca(2+) channels, while econazole inhibited both SOC channels and voltage-operated Ca(2+) channels with an equivalent range of IC(50) values. YM-58483 potently inhibited IL-2 production and NF-AT-driven promoter activity, but not AP-1-driven promoter activity in Jurkat cells. Moreover, this compound inhibited delayed-type hypersensitivity in mice with an ED(50) of 1.1 mg/kg. Therefore, we concluded that YM-58483 was a novel store-operated Ca(2+) entry blocker and a potent immunomodulator, and could be useful for the treatment of autoimmune diseases and chronic inflammation. Furthermore, YM-58483 would be a candidate for the study of capacitative Ca(2+) entry mechanisms through SOC/CRAC channels and for identification of putative Ca(2+) channel genes.